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Systemic effects of inhaled corticosteroids are milder in asthmatic patients than in normal subjects

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Inhaled glucocorticosteroids are the first line anti-inflammatory agents for the long term treatment of asthma.[1 2] They are also frequently prescribed in chronic obstructive pulmonary disease (COPD),[3] even if their efficacy in this condition is still controversial.[4]

The inhalatory mode of administration maximises the delivery to the airways and minimises the systemic delivery of glucocorticosteroids, increasing the therapeutic ratio.[5] However, long term treatment of asthma[6] and COPD[7] with inhaled corticosteroids is associated with a significant risk of dose related systemic adverse events. This risk is particularly worrying in patients with moderate to severe asthma who require continuous treatment with high dose inhaled steroids to keep the disease under control and to prevent exacerbations, and who also require recurrent cycles of systemic glucocorticosteroids to treat exacerbations.[2 3] The biomarkers most frequently used to assess systemic availability of glucocorticosteroids are serum cortisol, urinary cortisol and its metabolites, and serum osteocalcin. The most worrying potential systemic effects are osteoporosis, growth suppression, adrenal insufficiency, cataracts, and glaucoma.[8]

Several studies have assessed the systemic activity of inhaled steroids by looking at short term effects in normal subjects and/or mild asthmatics, with the assumption that results obtained in normal subjects could be transferred to more obstructed subjects such as those with moderate to severe asthma.[8] By contrast, recent studies have clearly shown that the systemic availability of inhaled glucocorticosteroids, and particularly fluticasone, is substantially less in patients with moderate to severe asthma than in normal subjects,[9] which suggests that results obtained in normal subjects (and perhaps asthmatic subjects with normal lung function) should not be used to predict systemic activity in patients with moderate to severe asthma. Inhaled steroids such as budesonide and fluticasone are potent locally and are almost entirely transformed into inactive metabolites in the liver, so that their systemic bioavailability is almost entirely due to their absorption by the lung.[5] The absorption through the lung depends on several factors, including mode of inhalation, particle size of the aerosol, and degree of airflow limitation of the subjects examined.

In this issue of *Thorax* Harrison *et al*[10] report that the systemic availability of inhaled fluticasone is higher in normal subjects than in patients with moderate to severe asthma, confirming that normal subjects are more sensitive than asthmatics to the systemic effects of this inhaled glucocorticosteroid. In fact, they found that treatment for 7 days with 1 mg/day inhaled fluticasone led to lower total cortisol metabolites in normal subjects than in those with asthma. They also found that budesonide was not associated with more systemic effects in normal subjects, suggesting that differences in the response may also be related to the type of steroid used.

The study certainly provides interesting results of clinical relevance. Indeed, it is reassuring to learn that patients with moderate to severe asthma—who require larger doses of inhaled steroids and, specifically, of fluticasone which has been shown to be particularly effective in patients with moderate to severe asthma[11]—are at lower risk of systemic effects. This reassuring message is in contrast to previous messages, mostly derived from studies in normal subjects, that suggested 4–5 times more systemic availability of fluticasone than of budesonide.[8] The merit of the study by Harrison *et al*[10] is that it clarifies the discrepancies of previous studies by showing that these discrepancies were the result of the different types of subjects examined and also, at least in part, of the use of different glucocorticosteroids.

The second important clinically relevant message of this study is that the larger systemic availability of fluticasone in normal subjects would suggest that fluticasone should not be used at high doses in asthmatic subjects with preserved lung function and that its dose should be reduced as lung function improves. Thus, fluticasone should be preferred in patients with moderate to severe asthma, not only because it is effective but also because it has similar systemic availability to budesonide and less effect on bone metabolism.

The larger effect of budesonide on osteocalcin suggests a higher risk of osteoporosis and fractures in patients treated with high dose budesonide. However, this effect was seen at doses of budesonide that are recommended only in patients with moderate to severe asthma. Indeed, long term treatment with regular doses of inhaled budesonide has

recently been shown to be devoid of significant effects on growth in children with asthma.[12 13]

The study by Harrison *et al*[10] has some limitations and its conclusions need some consideration. The doses of fluticasone and budesonide used in the study were not equivalent as fluticasone has been shown to be at least twice as potent as budesonide and thus the better efficacy of fluticasone after 4 weeks of treatment simply reflects the different potency of the two steroids.[2 5 8] Also, the two steroids were delivered through their respective devices which have markedly different characteristics.[14 15] Indeed, the smaller proportion of low fine respirable particles delivered by the Diskus might contribute to the lower lung absorption in asthmatic patients with obstructed airways. Finally, baseline values of urinary total cortisol metabolites were lower in asthmatic patients than in normal subjects as the asthmatic patients were already receiving regular treatment with inhaled steroids. Thus, it is possible that the larger systemic effect observed in normal subjects is, at least in part, related to higher baseline values, and that a similar initial effect might be observed in asthmatic subjects before starting treatment with inhaled corticosteroids.

The main message of the study of Harrison *et al*[10] is that systemic bioavailability of steroids should not be assessed in normal subjects but rather in subjects with asthma of different severity using a sensitive biomarker of systemic availability—their suggestion is to use urinary total cortisol metabolites. An important question is whether this marker is useful, not only in predicting the systemic effects associated with long term treatment with high dose steroids in a group of asthmatic subjects, but whether it may also predict the risk of systemic effects of inhaled steroids in individual patients.

Taking into account the fact that high doses of inhaled steroids are the most effective treatment for moderate to severe asthma, we badly need an early marker of systemic availability to be used in individual patients to predict the risk of systemic effects.

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